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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,016	10/29/2003	Ralph A. Casale	BP0206US-CN1	7084

23544 7590 08/17/2007

APPLIED BIOSYSTEMS
500 OLD CONNECTICUT PATH
FRAMINGHAM, MA 01701

EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
08/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,016	CASALE ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,41 and 75-110* is/are pending in the application.

4a) Of the above claim(s) *78,79,81,85,86,92,94-96,101,102,104,108 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,41,75-77,80,82-84,87-91,93,97-100,103,105-107 and 110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/07 and 6/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 28, 41 and 75-110 are pending in the instant application; claims 78, 79, 81, 85, 86, 92, 94-96, 101, 102, 104, 108 and 109 are withdrawn from consideration; claims 28, 41, 75-77, 80, 82-84, 87-91, 93, 97-100, 103, 105-107 and 110 are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on April 19, 2007, and June 28, 2007, have been considered by the Examiner. The submissions are in compliance with the provisions of 37 CFR § 1.97, except for reference "CCR" which does not include a proper citation of the title, source of publication, or date. Enclosed with this Office Action are return-copies of the Forms PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Previous Objections and Rejections

Any objections or rejections to the claims in the previous Office Action not reiterated in the instant Office Action are considered withdrawn from consideration.

Objection to the Abstract Under 37 C.F.R. § 1.72 - Maintained

The objection to the abstract of the disclosure because it does not allow the public generally to determine quickly from a cursory inspection the nature and gist of the invention, is maintained.

Applicants allege that their current abstract allows for the public to determine quickly based on a cursory inspection the nature and gist of the technical disclosure, and provide certain internet-published definitions of the terms "gist," "essence" and "nature."

Applicants' arguments have been fully considered, but are not found persuasive.

Instead, Applicants' attention is directed to MPEP § 608.01(b), where the examples are provided in understanding what 37 CFR § 1.72(b) means by "gist" and "nature". For example, for inventions directed to methods of making, the MPEP instructs that the abstract should include

the steps, the type of reaction, the reagents and process conditions generally stated. In this way, the public is able to determine the nature and gist of the technical disclosure, not by a broad-sweeping summary of an area of art, such as a brief statement that directs attention to combinatorial chemistry with PNA monomers in general, as Applicants have provided.

Applicants should amend the abstract so that it corresponds to at least one independent claim. For example, Applicants should describe the steps of a) through e) in either claim 28 or claim 41. *See* 37 C.F.R. § 1.72. Should Applicants amend the claims in their next reply, the amended abstract should take into account any further limitations added to the broadest independent claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 110, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 110 is indefinite for reciting the phrase "as soon as is practical" because one of ordinary skill in the art would not be able to determine the metes and bounds of this limitation. Neither the specification nor the relevant art teaches what is considered "practical" and what is not considered "practical," and further how long would one consider the appropriate time to determine practicality.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The newly presented phrase "substantially all" is new matter:

Claims 28, 75-77, 80, 82-84, 97-100, 103, 105-107 and 110, are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Amended claim 28 and newly presented claim 97, and all claims dependent therefrom, are rejected for the introduction of new matter by the phrase "substantially all," which now further limits the amount of base-labile N-terminal amine protecting groups that are removed.

Applicants provide certain remarks regarding their amendments to claim 28, however, none of the remarks address this particular amendment.

Upon review of the specification, the phrase "substantially all" does not find support in the specification, either by way of literal recitation, reasonable interpretation of certain description, working example or the claims as originally provided. For example, in paragraph 0113, Applicants disclose:

> "The solid support is then treated for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support bound first PNA monomer."

Specification, paragraph 0113. Such a statement is not equivalent to the current claim language found in claims 27 or 97. Something that "substantially removes" does not equate to an "almost complete removal" as the current claim language would suggest.

Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection over Breipohl, Kovacs, Thomson and Koch, is maintained:

The rejection of claims 28, 41, 75-77, 80, 82-84, 87-90, 93 and 110, under 35 U.S.C. § 103(a) as being unpatentable over Breipohl *et al.*, U.S. Patent No. 6,121,418, issued on September 19, 2000, in view of Kovacs *et al.*, Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4htm, September 1, 2000, and Thomson *et al.*, *Tetrahedron 51*:6179-6194 (**1995**), and Koch *et al.*, *J. Peptide Res. 49*:80-88 (**1997**), is maintained. This rejection is extended to newly presented claims 97-100, 103, 105-107 and 110, which have the same added limitations of rejected claims 28, 75-77, 80 and 82-84.

Applicants traverse the rejection and allege that the rejection is improper because it is based on impermissible hindsight, and does not demonstrate a reasonable expectation of success in arriving at the claimed invention based on the cited references (Reply, page 13). Applicants continue to allege that none of the references teaches their claimed time period of 1 to 2 minutes, and assert that the references are non-analogous art (Reply, pages 14 and 15).

Applicants further purport that the rejection is improper because since Koch was aware of Thomson's disclosure, as was Kovacs, yet none explicitly recited 1 to 2 minutes, the invention cannot be obvious as limitation that is routinely adjusted. Applicants are also of the opinion that the rejection based on such references amounts to an 'obvious-to-try' approach.

Applicants' arguments have been fully considered, however, are not found persuasive.

The scope of the claimed invention:

As stated previously, claim 28 is directed to a method for forming a support bound PNA dimer, said method comprising: a) coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker wherein the PNA monomer comprises a N-terminal amine base labile protecting group; b) optionally washing the

solid support to remove excess first PNA monomer; c) treating the solid support for a period of about 1 to about 2 minutes with a deprotection reagent that substantially removes the base labile N-terminal amine protecting group from the support; d) washing the solid support to remove the deprotection reagent; and e) coupling a second PNA monomer to the N-terminal amine of the first PNA monomer after performing steps (c) and (d). New claim 97 is similar.

The scope of the cited references:

Contrary to Applicants allegations, each of Briepohl, Kovacs, Thomson and Koch, are considered analogous art in the context of the pending claims. Each is related to methods for synthesizing chemically protected PNA monomers on solid supports. Although there are certain differences between each, Applicants have failed to consider the references as whole from the perspective of those of ordinary skill in the art.

Breipohl teaches a method for synthesizing PNA oligomers on a solid support, wherein the PNA monomer comprises a N-terminal amine base labile protecting group, and the solid support is a rink-type resin (col. 5, lines 25-26, in reference to prior art disclosure H. Rink, *Tetrahedron Letters* 1987, 3787-3790).[1] The group in Rink meet the limitations of the sterically hindered acid forming cleavable linker, and the trityl chloride resin of claim 82, 83 and 84 (regarding claim 84, Breipohl's commercially available resin, such as the Rink resin, provides greater than 0.08 mmol per gram); also meets the limitations of claim 93. Breipohl also teaches treating the solid support with deprotection reagents:

> "Examples of reagents for eliminating the base-labile amino protecting group PG are a solution of piperidine, morpholine, hydrazine or 1,8-diazabicyclo[5.4.0]undec-7-ene (***DBU***) in diinethylformamide, N-methylpyrrolidinone (***NMP***), acetonitrile (ACN) or dichloromethane

[1] Since Rink is effectively incorporated by reference, in particular the teachings as it pertains to PNA suitable resin supports, Breipohl is treated as teaching these limitations. *See, Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which [page 1680] is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

> (DCM); the use of 20% piperidine in DMF or N-methylpyrrolidinone and also of a mixture of ***2% DBU*** and 2% piperidine in DMF or 0.1M DBU in DMF or 0.1M DBU in dichloromethane is particularly preferred for the Fmoc, Dnpeoc and Bnpeoc protecting groups."

Breipohl, col. 7, lines 22-33 (emphasis added). Accordingly, the limitations of claim 80 are taught. Breipohl also teaches the coupling of subsequent PNA monomers, *i.e.*, oligomers (col. 1, lines 28-32). Breipohl also teaches a number of base labile protecting groups, such as Fmoc and Bnpeoc (Breipohl, col. 6, lines 1-15).

Breipohl also teaches using acid labile protecting groups, as in claim 41:

> Protecting groups which are compatible with the base-labile amino protecting group PG, such as, for example, protecting groups, which are ***labile to weak or medium strength acids, of the urethane type, such as tertbutyloxycarbonyl (Boc), 4-methoxybenzyloxycarbonyl (Moz)*** or 3,5-dimethoxyphenyl-2-propyl-2-oxycarbonyl (Ddz), or of the trityl type, such as triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)-diphenylmethyl (Mtt), di-(4-methoxyphenyl)phenylmethyl (Dmt) or 9-(9-phenyl)xanthenyl (pixyl) are used for protecting the exocyclic amino function in the nucleotide bases B' which are protected in their exocyclic amino function. The use of butyloxycarbonyl (Boc), triphenylmethyl (Trt), (4-methoxyphenyl)diphenylmethyl (Mmt), (4-methylphenyl)diphenylmethyl (Mtt) or di-(4-methoxyphenyl)phenyl-methyl (Dmt) is particularly preferred, with Trt, Mtt, Mmt and Dmt surprisingly effecting a marked improvement in the solubility of the monomers. The use of (4-methoxyphenyl)diphenylmethyl (Mmt) is very particularly preferred."

Breipohl, col. 7, lines 3-23 (emphasis added). As in claims 87-89, Breipohl also teaches benzyloxycarbonyl (*i.e.*, Bhoc or Z; col. 12, line 63), and teaches t-boc (*i.e.*, Boc), Mmt and Fmoc, and suggests that these groups may be used in many combinations for protection. As in claim 90, Breipohl suggests the nucleobase adenine and cytosine.

Although Breipohl teaches numerous base-labile protecting groups and deprotection approaches, Breipohl does not explicitly state that a period of about 1 to about 2 minutes is the deprotection time, as in claim 28 and new claim 97. However, as set forth in the previous Office Action, this deficiency is remedied by Kovacs, Thomson and Koch.

Applicants allege that Kovacs is non-analogous art, however, Applicants' comments miss the mark. Kovacs teaches a method of synthesizing PNA oligomers on a solid phase. As part of

the method, Kovacs teaches the removal of the N-terminal amine protecting group in five minutes intervals (see Scheme 2). Applicants seem to be of the opinion that the fact that Kovacs teaches 2 x 5 minutes is more relevant than a teaching of 5 minutes because it equates to ten minutes. Nonetheless, Kovacs teaches 5 minutes, and Applicants claims do not preclude incremental deprotection steps since the claim language "comprising" is used. For example, Applicants claims still read on a total of 10 minutes, such as 10 x 1 minute deprotection treatment, or a 5 x 2 deprotection treatment.

Kovacs then teaches coupling a first PNA monomer to a solid support (NovaSyn hydroxy-Tentagel resin) comprising an acid forming cleavable linker, wherein the PNA monomer comprises base labile N-terminal protecting groups (*i.e.*, Boc/Z and Fmoc/Z).

Applicants provide similar commentary regarding Thomson, because Thomson teaches a 3 x 5 minute deprotection scheme on the solid phase. Still, Thomson teaches PNA oligomer synthesis on resins. Thomson also teaches a modified deprotection reaction of the Fmoc-on PNA compound after it has been freed from the resin. Specifically, Thomson teaches deprotection with piperidine at an adjusted concentration, at a different temperature, and for different length of time (see page 6193).

Applicants continue to challenge the rejection by stating the Koch is non-analogous art (page 15 and 16), and assert that a combination of Kovacs and Thomson, in combination with Koch is "like comparing apples to oranges," on page 16 of the Reply.

Again, Applicants comments miss the mark. Although Koch is primarily focused on the use of acid-labile protecting groups (such as those of claim 41), Koch directly acknowledges what is known in the art by those who practice using base-labile PNA amino protecting groups (as in claim 28):

> "It is now apparent that the chemical structure of the PNA monomer sets certain limits to the choice of optimal oligomerization strategy. ***Basic media promotes side reactions of PNA oligomers*** with liberated ***primary amines must be treated in the shortest possible time with a minimal amount of base***."

Koch, page 80, col. 2, first full paragraph (emphasis added).

Accordingly, Koch teaches that when using protected amines in PNA chemistry, careful selection of the base reaction conditions must be taken into consideration to avoid cyclization.

This indeed is a very clear teaching that specifically suggests what actions can be taken in this art to avoid the pitfalls of cyclization, and produce an optimized solid-phase immobilized PNA oligomer using base-labile protecting groups.

Applicants further allege that if the selection of 1 to 2 minutes was obvious based on the art cited by the Examiner, that Kovacs or Thomson would have themselves arrived at a teaching of about 1 to about 2 minutes (*e.g.*, as if all teachings in the art should be anticipatory to meet the obviousness standard). Applicants pose the question:

> "So all this all begs the question, if it was long-known that basic conditions cause decomposition of a PNA oligomer and therefore should be minimized, why did the art teach treatment for 10-15 minutes and not 1-2 minutes for the removal of the Fmoc protecting group?"

Reply, page 16.

However, Applicants' inquiry as a test for an obviousness determination is neither proper nor the legal standard adopted by the courts, and is therefore inapposite.

Instead, the facts of the instant case and the conclusion of obviousness made by the Examiner are similar to the facts and decision of the Court in, *Syngenta Seeds, Inc., v. Monsanto Co.*, (Fed. Cir. 2007), opinion decided on May 3, 2007 (this opinion is non-precedental). In this case, the Court found that claims directed to a transgenic corn plant that produces the Bt protein, having a foreign DNA nucleic acid coding sequence with a G+C content of at least about 60%, to be obvious in view of the Barton reference. Barton taught that Bt expression is improved through the use of codons preferred by the native plant, that Bt has a high proportion of A+T codons, but that plants generally have a bias towards codons rich in G+C.

Syngenta argued that although the general teaching for substituting G+C codons may have been obvious, that the "*more than 60%*" limitation would not be obvious. The Court disagreed, and replied:

> "It is true, as Syngenta argues, that the quoted portion of the Barton application suggests that positive results could be achieved without modifying the entire DNA sequence. But the entire quoted statement [in Barton], including the conclusion that a complete codon substitution "might still be expected to increase efficiency of expression," plainly constitutes a suggestion that some increased efficiency of expression could be achieved by producing a synthetic Bt gene with a coding region consisting entirely of plant-preferred codons."

Id., page 5.

Syngenta also argued that numerous other prior art references failed to meet the "G+C content of greater than 60%." However, the Court ruled that such a fact did little to offset Barton's clear suggestion that complete codon substitution would lead to improved results (*Id.*, pages 7 and 8). This is similar to Applicants alleged arguments that none of the references teach the about 1 to 2 minutes.

For certain recent precedent rulings from the Federal Circuit regarding the "reasonable expectation of success" standard, Applicants attention is directed to *Alza Corp., v. Mylan Laboratories, Inc.*, 80 USPQ2d 1001 (Fed. Cir. 2006), wherein the Court found certain pharmaceuticals obvious because the art provided articulated reasoning supported by some level of rational underpinning. See also, *Ex parte Kubin*, 83 USPQ2d 1410 (BPAI 2007), where the Board ruled a claimed nucleotide sequence obvious because the prior art pointed the ordinary artisan in the appropriate direction, with an idea of what was important regarding certain protein sequences and how one would know how to produce/identify the corresponding nucleotide sequence (*i.e.*, a reasonable expectation of success).

However, Koch clearly provides a suggestion that modifying reaction time and/or modifying base strength of during the deprotection step can improve results. It is uncertain how Applicants can be of the opinion that Koch is non-analogous art, especially when Koch explicitly suggest that deprotection reaction times with base-labile protecting groups should be kept as short as possible. Regardless, reducing the deprotection time from 5 minutes as in Kovacs and Thomson, to "to about 2 minutes" is only "about cutting the time in half"; hardly a stretch when reducing deprotection time is *explicitly suggested* by Koch.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Breipohl, Kovacs, Thomson and Koch are related to methods for preparing PNA oligomers on solid phases in a step wise manner, wherein the PNA monomers are added to the resin in protected form, followed by a deprotection step. The N-terminal base labile protecting groups of Breipohl and Kovacs are similar, and in some instances, both teach Fmoc, a protecting group that each teaches can be removed with piperidine in DMF, as well as the use of other deprotection reagents. Although Kovacs teaches 5 minutes

in Scheme 2, one of ordinary skill in the art would have recognized from the teaching of Kovacs that deprotection times of this type typically require a couple minutes to complete, and are parameters that are routinely adjustable. As clearly conveyed previously, such an understanding is evidenced by Koch and Thomson, (see Koch, page 81, col. 1, lines 1-20; and page 81, col. 2, lines 10-15, wherein 3 minutes are taught; see Thomson on page 6192, last paragraph). Absent any secondary considerations of nonobviousness, the limitation of about 1 to 2 minutes is an obvious variation of the times taught by Kovacs and/or Koch, and is considered routine experimentation. Therefore, the claimed invention as a whole was *prima facie* obvious at the time it was made.

Applicants are further of the opinion that claim 41 is not obvious, because the limitation of the surface loading is not explicitly taught by the references. This is not correct.

Breipohl teaches a method for synthesizing PNA oligomers on a solid support, and the composition, wherein the PNA monomer comprises a N-terminal amine base labile protecting group, and the solid support is a rink-type resin (col. 5, lines 25-26, in reference to prior art disclosure H. Rink, *Tetrahedron Letters* 1987, 28:3787-3790).[2] The group in Rink meet the limitations of the sterically hindered acid forming cleavable linker. Regarding the resin loading, Breipohl's commercially available resin, such as the Rink resin, provides greater than 0.08 mmol per gram, such as 0.4 mmol/g (see Rink, page 3788). Furthermore, Breipohl contemplates the inefficiency and recognizes the issues with dimer loading:

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[2] Since Rink is effectively incorporated by reference, in particular the teachings as it pertains to PNA suitable resin supports, Breipohl is treated as teaching these limitations. *See, Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which [page 1680] is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

> "After eliminating the base-labile protecting group of the structural component coupled to the resin using a suitable reagent as described above, the subsequent, protected structural components (PNA monomers and amino acid derivatives) are coupled on, one after the other, in the desired sequence. The PNA resins which arise as intermediates and which are protected at the N terminus with a base-labile protecting group are unblocked by the previously described reagents before they are linked to the subsequent PNA monomer.
>
> The coupling or activation of the amino acid derivatives with one of the abovementioned activating reagents can be carried out in dimethylformamide, N-methylpyrrolidinone, acetonitrile or methylene chloride, or a mixture of the said solvents. The activated derivative is customarily employed in a 1.5 to 10 fold excess. In those cases in which incomplete coupling occurs, the coupling reaction is repeated without unblocking the amino group of the structural component which has just been coupled on."

Breipohl, col. 10, line 56 through col. 11, line 7. Breipohl also uses the same reagents and solvent as Applicants (see Figures 2-4 in specification, and compare to cols. 5-13 of Breipohl).

Also meeting the limitations of claim 1, is the disclosure of Breipohl's TGA resin with 4-(4'-methoxybenzhydryl)phenoxybutyric acid or 4-hydroxymethylphenoxyacetic acid linkers with the coupled PNA dimers/oligomers (col. 5, lines 18-67).

Also meeting the limitations of claim 41, is the disclosure of Breipohl's 2-chlorotriphenylmethyl resin (col. 5, lines 18-67)[3]. Accordingly, there are numerous instances where the claimed surface loading is met by the references.

Claims are obvious over Seitz, Thomson and Koch:

The rejection of claims 28, 75 and 77, rejected under 35 U.S.C. § 103(a) as being unpatentable over Seitz, *Tetrahedron Letters 40*:4161-4164 (**1999**), in view of Thomson *et al.*, *Tetrahedron 51*:6179-6194 (**1995**), and Koch *et al.*, *J. Peptide Res. 49*:80-88 (**1997**), is maintained. This rejection is extended to newly presented claims 97, 98 and 100, which have the same added limitations as claims 28, 75 and 77.

[3] As evidence of this limitation, see Bollhagen (Bollhagen, et al. (1994) J. Chem. Soc., Chem. Commun., 2559-2560) which shows the structure of the oligomer attached 2-chlorotriphenylmethyl resin; additional evidence of loading in claimed range is shown by Eda *et al.*, *Tetrahedron Letters 42*:2063-2068 (**2001**).

Applicants submit similar arguments as to why the rejection of the invention is not obvious over Seitz, Thomson and Koch. Effectively, Applicants are of the opinion that the "about 1 to about 2 minutes" is not explicitly disclosed by any of the references.

However, this argument is unpersuasive for the reasons presented above, namely, the explicit suggestion to modify deprotection times in Koch, and the Court's opinion in *Syngenta.*

As in claim 28, Seitz teaches a method for forming a support bound PNA oligomer, including dimers. In scheme 4, and description thereof, Seitz teaches coupling a first PNA monomer to a sterically hindered solid support comprising a sterically hindered acid forming cleavable linker (HYCRON resin; *i.e.*, the double bond is sterically hindered, and upon ozonolysis and peroxide treatment, alkene groups form an organic acid group), wherein the PNA monomer comprises a N-terminal protecting group. Subsequent PNA monomers are added sequentially to the resin to form a surface attached PNA oligomer. As in claims 75 and 77, Seitz teaches Fmoc/Bhoc protected PNA oligomer synthesis, wherein the nucleobase protecting group is Fmoc (page 4163, paragraph positioned directly above Scheme 4, last sentence). As in claim 76, Seitz teaches a PNA with a cytosine nucleobase.

Although Seitz teaches certain important reaction conditions, Seitz does not explicitly provide the reaction times for the deprotection step, such as Applicants about 1 to about 2 minutes and reference to cyclization, found in claim 28.

Thomson, a teaching referenced by Seitz (reference number 11), teaches PNA oligomer synthesis on resins. Thompson teaches a deprotection step that is carried out at 3 x 5 minutes.

Koch, who also references Thomson (reference number 11), teaches that when using protected amines in PNA chemistry, careful selection of the base reaction conditions must be taken into consideration to avoid cyclization (first and second columns on page 80).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Seitz, Thomson and Koch, are related to the synthesis of chemically protected PNA oligomers on resins, wherein the protected oligomers are deprotected with a base in an organic solvent. One of ordinary skill in the art would have been motivated by the teachings of Thomson and Koch to ensure that cyclization was kept to reasonable levels, such as less than 50%, and would have recognized the reaction time

adjustments in the range of about 1 to about 2 minutes as a matter of routine experimentation. Therefore the claimed invention as a whole was *prima facie* obvious at the time it was made.

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JSL/

/Jon D. Epperson/
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